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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,021	03/19/2002	Philippe Gabant	VANM243.1APC1	5739

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EXAMINER	
NGUYEN, DAVE TRONG	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/031,021	GABANT ET AL.	
	Examiner	Art Unit	
	Dave T Nguyen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) *9 and 11-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 4/12/10
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicant's election without traverse of Group I claims, claims 1-7 and 10, in the response filed December 17, 2003 is acknowledged.

Claims 9, 11-13 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claimed invention.

Claims 1-7, and 10, are pending for examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, and 10, readable on a genus of non-human mammal, which have been genetically modified so as to render a mutation, a partial deletion or a total deletion in the genetic sequence encoding the endogenously wild-type alpha-fetoprotein (AFP), are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The main thrust of the claimed invention is applicant's discovery of a nexus between a murine AFP and its role for female production and fertility (page, 3, par. 006). This discovery was based on the making of AFP knock-out mice (par. 008, working

examples, wherein recombinant ES cells carrying the targeted allele were injected in C57BL/6J blastocysts (par. 0019), and wherein both heterozygous embryos and homozygous embryos/mice were produced. As the result of the making of these AFP knock-out mice, and further intercrosses, applicant has observed and concludes, particularly on the basis of AFP knock out homozygous mice and their subsequent intercrosses (page 9), that no pugs were obtained from this intercrosses, thereby suggesting an essential role of AFP for development and/or fertility (Table 2). Page 9 further states that "males homozygous for an *afp* disrupted allele appeared fertile and sired offspring but homozygous females never produce any live offspring". An histological analysis was done on the AFP knock out homozygous females (*afp* $^{lacZ1/lacZ1}$) shows that (page 10) their homozygous tissues do not contain corpus lutea, the lack of which is indicative of the absence of ovulation (Figure 4). On the basis of this finding, Applicant further suggests on page 14 that "the *afp-/-* phenotype corresponds to alive sterile females, which is a phenotype that may exist in the mouse population as well as in the human population.

A review of the entire as-filed specification, as illustrated above, shows that the specification does not sufficiently describe a representative number of species of non-human mammals as claimed. The factual premises of the description analysis for a genus of the claimed non-human mammals are at least 1/ the knowledge and detailed information as to the sequence structure of the AFP gene present in each of the non-human mammalian species as clearly embraced by the claimed. This sequence structure is necessary in order to recombinantly knock out the AFP gene endogenously

expressed in ES cells obtained from each of the non-human mammal; and 2/ the availability of the ES cells obtained from at leas a representative number of non-human mammalian species such as dogs, sheep, pigs, horses, monkeys, cats, tigers, cows. The disclosure in the as-filed specification with respect to at least 1/ and 2/ must be adequate to enable possession of the desired subject matter.

The claimed invention further encompasses an enormous number of partially deleted AFP or mutant APF expressed in a non-human mammal, wherein neither their sequence structure nor their biological activities have not been demonstrated. The claimed invention is attempted to claim genetically modified ES cloned non-human mammals, which are yet to be identified at the time the invention was made. Applicant's disclosure of a AFP knock out mouse, and/or potential techniques for making other claimed transgenic non-human mammals, does not provide sufficient description of the structures of a representative number of the transgenic non-human mammals as claimed. In other words, it is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims, requires more than a mere statement that it is part of the invention and reference to potential methods and/or assays for isolating the variants; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of such claimed genus. A disclosure of no more than the AFP knock out mice (*afp* $^{lacZ1/lacZ1}$), as in the instant case, is simply a wish to know the identity of other genetically modified non human mammals as claimed. The state of the art exemplified by Houdebine (J. of Biotechnology 98, 145-160, 2002) states (page 149):

> Homologous recombination is a rare event. Cells in which it occurred must be selected and further used to generate a living embryo. This proved to be feasible on condition to use embryonic stem cells capable of forming chimeric embryos after microinjection into blastocysts or morula (Viville, 1997). Although laborious this protocol has become popular and genes are frequently inactivated in mouse. Despite repeated efforts, the extension of this method to species other than mouse failed. This is clearly due to the fact that the recombined ES cells have more or less the capacity to participate to the development of chimeric embryos but that transmission of the mutation to progeny has been observed so far only in two mouse lines and essentially of the 129/SV line (Smithies, 2001). For years, it was admitted that mouse as the model for the use of ES cells to mutate genes in a targeted manner. The systematic lack of success met in rat, rabbit, chicken, pig, sheep and cow now inclines to consider that the so-called ES cells cannot be used for the germinal transmission of a mutation except in two mouse lines systematic studies to tentatively identify genes involved in the two mouse lines are in course.

In addition and with respect to claims readable on numerous non-human mammals other than the mouse species, since differences in expression among lines of animals are caused by "position effect", and since host cell sequences at the site of integration can modify the regulation of the transgene both qualitatively and quantitatively, position effects where the transgene is influenced by its site of integration in the host chromosome can have major consequences on the expression of the transgene, including loss of cell specificity, inappropriately high copy number-independent expression and complete silencing of the transgene (Polejaeva *et al.* (Theriogenology, Vol. 53, pages 117-126, 2000). More specifically, Polejaeva *et al.* states:

> Transgenic animals can be successfully produced in a number of species including mice, rabbits, pigs, sheep cattle, and goats by the injection of the gene of interest into the pro-nucleus of a zygote. However, this technique suffers from several serious limitations. The most profound is that DNA can only be added, not deleted, or modified in situ. Also, the integration of foreign DNA is random; this could lead to erratic transgene expression due to the effects at the site of incorporation. In addition, with random integration the possibility exists for the

> disruption of essential endogenous DNA sequences or activation of cellular oncogenes, both of which would have deleterious effects on the animal's health. Finally, transgenic animals generated using pro-nuclear microinjection are commonly mosaic, i.e., an integrated transgene is not present in all cells. Therefore, the production of the required phenotype coupled to germ line transmission could undue experimentation. See page 119.

Thus, it is not apparent how one skilled in the art envisions a genus of the non-human transgenic mammal as broadly claimed. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which is not conventional in the art as of applicants effective filing date. Claiming mutant or partially deleted DNA, and/or transgenic clones associated with any phenotype, which are broadly defined by the as-filed application, without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of the phenotypic transgenic clones other than the mouse species, wherein the AFP gene was completely deleted, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Thus, it is not apparent to one skilled in the art as to how claims encompassing a genus of transgenic clones

embraced by the claimed methods and products, find an adequate support from this instant disclosure at the time the invention was made.

Claims 1-7, and 10 are rejected under 35 U.S.C. 112, first paragraph, because the specification is only enabling for claims limited to:

1/ A genetically modified female mouse, whose genome comprises a homozygous mutation, a partially homozygous deletion or a totally homozygous deletion in the endogenous genetic sequence encoding the wild- type alpha-fetoprotein (AFP), wherein said genetically modified female mouse does not express a functionally active AFP, is sterile, and does not undergo a menstrual cylclization.; and

2/ A method for identifying a candidate agent for use in treating osteoporosis, increasing fertility, or preventing conception comprising:

contacting the genetically modified female mouse of 1/ with a candidate agent;

determining the effects of said agent on osteoporosis, fertility or conctraception in said genetically modified female mouse.

The specification is not enabling for claims directed to any other claimed embodiment within the elected claimed invention. The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731,

8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Specifically, since the claimed invention is not supported by a sufficient written description, particularly in view of the reasons set forth above, one skilled in the art would not known how to make and use the claimed invention as broadly claimed so that it would operate as intended by the disclosed as-filed application.

In addition, the specification coupled with knowledge in the prior art does not provide sufficient guidance and/or evidence for one skilled in the art to make and use the claimed invention readable on even an AFP knock-out male mouse, without any undue experimentation, particularly on the basis of applicant's disclosure.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

As the first issue, while the state of the art of transgenics is such that one skilled in the art can deliver and express a gene in a desired animal, it is not reasonably

predictable for one skilled in the art to produce a transgenic non-human mammal (other than a mouse) that exhibit a desired phenotype. Applicants contemplates that by employing ES cells via homologous recombination to produce an embryo with useful polypeptides as intended by the as-filed application. At the time the invention was made, the art of transgenics including gene targeted modification using ES cell technology was known to be unpredictable with respect to the efficacy of incorporation of transgene, levels of expression as a result of the incorporation, and the phenotypes expressed as a result of the transgene incorporation via homologous recombination in ES cells (Polejaeva *et al.*, Theriogenology, Vol. 53, pages 117-126, 2000; & Sigmund, 2000, Thromb Vasc Biol., 20:1425-29). More specifically, Polejaeva *et al.* states:

> Transgenic animals can be successfully produced in a number of species including mice, rabbits, pigs, sheep cattle, and goats by the injection of the gene of interest into the pro-nucleus of a zygote. However, this technique suffers from several serious limitations. The most profound is that DNA can only be added, not deleted, or modified in situ. Also, the integration of foreign DNA is random; this could lead to erratic transgene expression due to the effects at the site of incorporation. In addition, with random integration the possibility exists for the disruption of essential endogenous DNA sequences or activation of cellular oncogenes, both of which would have deleterious effects on the animal's health. Finally, transgenic animals generated using pro-nuclear microinjection are commonly mosaic, i.e., an integrated transgene is not present in all cells. Therefore, the production of the required phenotype coupled to germ line transmission could undue experimentation. See page 119.

Thus, it is not apparent as to how one skilled in the art, without any undue experimentation, makes and uses any transgenic animal which must exhibit a useful phenotype, particularly on the basis of applicant's disclosure.

To the extent that claims are readable on an AFP knock-out male mouse, and insofar as the only intended and enabling use of the claimed invention is the sterile

phenotype upon which a screening assay can be employed, it is not apparent how a skilled artisan employ any useful assay on a fertile genetically modified male mouse, particularly since there is no phenotypic difference whatsoever between the mouse mice and a wild-type male mouse, which difference is essential to make a determination whether or not a treatment effect can be generated in the claimed screening assay. As such, the claims are only reasonably enabling for claimed directed to the embodiments as indicated in the first paragraph of the stated rejection.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite in the recitation of "the genetic sequence encoding the wild type alpha-fetoprotein (AFP). The term does not contain an antecedent basis. Should applicant intend to mean that the endogenous AFP gene is knock-out then the claim should be amended to reflect the intended meaning. For example, a change to "...deletion in endogenous genetic sequence encoding the wild type alpha-fetoprotein (AFP) would obviate the rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Due to the extremely broad formulation of the independent claim 1, where claim 1 does not specify the phenotype of the transgenic mice as taught in the as-filed specification, but only that the modified mouse comprises a "mutation, a partial or total deletion in the genetic sequence encoding the wild type mammal alpha-fetoprotein", claim 1 is reasonably interpreted as broadly encompassing transgenic mice which comprise a mutation in the AFP gene and yet still exhibit the phenotype of a functional AFP.

As such, the following rejection is applicable:

Claims 1-4 are rejected as being anticipated by Jin *et al.,* PNAS, vol. 95, pp. 8767-8772, 1998, IDS, or Cirillo *et al.,* Developmental Biology, 168, pp. 395, 405, 1995, IDS).

Both Jin *et al.,* and Cirillo *et al.* teach a genetically modified mouse comprises a partial deletion of a genetic sequence encoding a functionally active alpha-fetoprotein (entire disclosures).

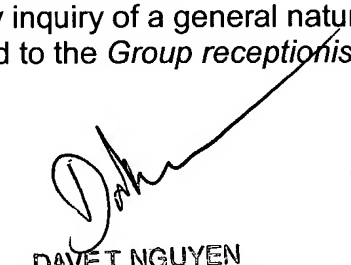
No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **571-272-0731**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Amy Nelson*, may be reached at **571-272-0184.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center number, which is **703-872-9306.**

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.



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